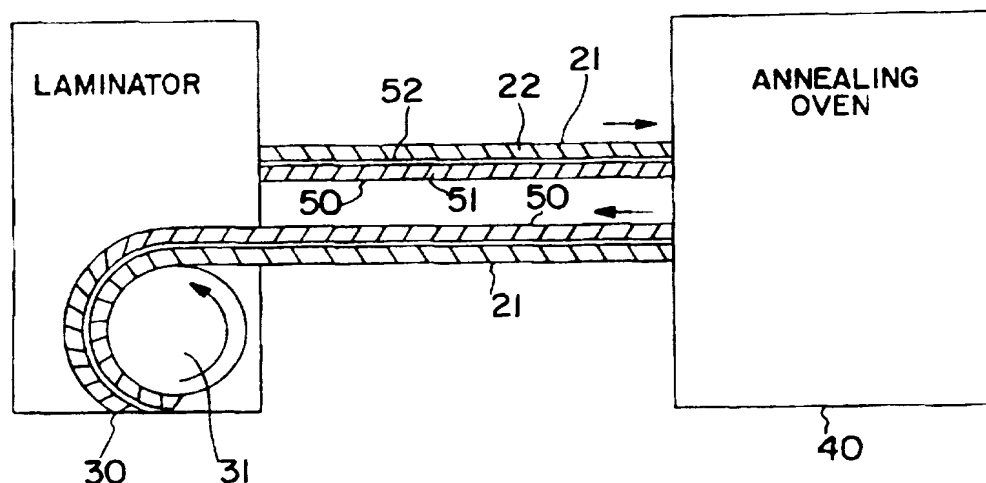




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(54) Title: IMPROVED METHOD FOR PREVENTING CRYSTAL FORMATION IN A DISPERSION OF A LIQUID IN A MATRIX



(57) Abstract

An improved method for the manufacture of transdermal drug delivery devices comprising liquid dispersions of a liquid in an aqueous or nonaqueous matrix is disclosed. More particularly, the invention relates to preventing the formation of a crystalline structure in such liquid dispersions by annealing films and laminates in-line immediately following film formation and/or lamination during the manufacture of these devices.

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1
2 IMPROVED METHOD FOR PREVENTING CRYSTAL
3 FORMATION IN A DISPERSION OF A LIQUID IN A MATRIX

4
5 FIELD OF THE INVENTION

6
7 This invention relates to the manufacture of dispersions of a liquid
8 in an aqueous or non-aqueous matrix and to drug delivery devices which
9 utilize these liquid dispersions. More particularly, the invention relates to
10 preventing the formation and/or growth of a crystalline structure in films or
11 laminates comprising such liquid dispersions by annealing the films and/or
12 laminates immediately following film formation and/or lamination. The crystal-
13 free films and laminates may then be formed into various articles, such as
14 drug delivery devices.

15
16 BACKGROUND OF THE INVENTION

17
18 As used herein, "annealing" refers to a process of subjecting the liquid
19 dispersion or article formed therefrom to a specified, elevated temperature for
20 a predetermined minimum period of time and then allowing the dispersion or
21 article to cool to ambient conditions.

22 Transdermal delivery devices comprising a dispersion of a drug or
23 other biological agent in various aqueous or non-aqueous matrices are known
24 in the art as described in U.S. Patent Nos. 3,598,122, 3,598,123, 4,031,894,
25 4,144,317, 4,201,211, 4,262,003, 4,379,454, and 4,436,741, all of which are
26 incorporated herein in their entirety by reference. As disclosed in these
27 patents, aqueous matrices typically comprise water or water/ethanol and
28 1-5 wt. % of a gelling agent such as hydroxyethylcellulose. Non-aqueous
29 matrices are typically comprised of a polymeric material such as copolymers
30 of ethylene vinyl acetate or blends of low molecular weight and high

1 molecular weight polyisobutene. The drug may be in solid form or in the form
2 of a liquid dispersion. This invention relates to such liquid drug dispersions.

3 In addition to the above mentioned patents, U.S. Patent No. 5,370,924,
4 incorporated herein in its entirety by reference, discloses methods for
5 manufacturing transdermal drug delivery devices. The methods disclosed in
6 this patent describe a process whereby the various elements of a transdermal
7 device may be fabricated separately and joined together in a final
8 manufacturing step.

9 Although this invention will be described hereafter specifically with
10 respect to scopolamine delivery devices, it should be recognized that it is
11 applicable to dispersions of any other drug or biological agent in matrices
12 where a crystalline structure may be formed. Such drugs or agents such
13 as nicotine, secoverine, and benztropine, for example, may, to the extent
14 they form crystalline structures, be treated in a manner similar to the
15 methods by which dispersions of scopolamine base are treated according
16 to this invention.

17 Transdermal delivery devices for the administration of scopolamine
18 of the type disclosed in U.S. Patent 4,031,894 cited above are used
19 extensively for the prevention of motion sickness. The original manufacture
20 of the product is described in the patent by solvent casting of chloroform
21 solutions of scopolamine base in polyisobutene (PIB) and mineral oil (MO)
22 onto impermeable webs to form drug reservoir and contact adhesive films.
23 Upon evaporation of the chloroform, a dispersion of liquid scopolamine
24 base in the PIB/MO matrix is formed. The drug reservoir and contact
25 adhesive films are then laminated to opposite sides of a release rate
26 controlling membrane, formed from a mineral oil impregnated microporous
27 film, to produce a final laminate comprising a removable release liner layer,
28 an adhesive layer, a rate controlling membrane layer, a drug reservoir layer,
29 and an impermeable backing lamina. The final laminate is then die cut into
30 individual systems and packaged in individual heat sealed pouches.

1 The manufacture of the product in this manner was carried out for
2 approximately five years without any indication of the formation of crystals in
3 either the drug reservoir or the adhesive. After that time, small crystals of
4 scopolamine hydrate were observed infrequently but this did not present a
5 problem because the release rate of the drug from the device was not
6 affected by the presence of the small number of small crystals then occurring.
7 In addition to the small number and size of the crystals, another reason that
8 the release rates were not affected is attributed to the observation that the
9 crystal size did not change appreciably (i.e. minimal if any crystal growth)
10 with time in the pouch.

11 Approximately two years later, larger numbers of rapidly propagating
12 crystals were observed in the drug reservoir, with a lower incidence observed
13 in the contact adhesive layer which contained a lower concentration of
14 scopolamine base. At that time, the size of the crystals and their frequency
15 of occurrence had increased to the point where they produced a significant
16 adverse effect on the release rate of scopolamine from the device.
17 Thereafter, every lot manufactured developed unacceptably high crystal size
18 and frequency and commercial production had to be halted until the problem
19 could be solved.

20 Crystallization was most noticeable after the step in which the final
21 laminate film was cut into individual devices. After the final laminate film was
22 fed through the die-cutting machine for the formation of individual transdermal
23 delivery units, crystallization began around the edges of the cut product and
24 crystalline growth thereafter propagated rapidly throughout the mass of the
25 reservoir and in some cases the adhesive layer. Visually observable crystals
26 were not necessarily apparent immediately after the cutting step; instead they
27 would typically develop over a period of days. These crystals were identified
28 as a hydrate form of scopolamine base.

29 Various attempts to eliminate the problem were tried over the next
30 several months, all to no avail. For example, the drug reservoir film, adhesive
31 film, and the final laminate film were heated overnight, yet crystallization after

die-cutting still occurred. Similarly, the casting solutions were heated and allowed to stand for extended periods also with no effect. Attempts to reduce the amount of residual water in the chloroform solution of the scopolamine base by drying with extra amounts of drying agents such as anhydrous sodium sulfate and magnesium sulfate were also unsuccessful as crystallization still occurred. Extensive cleaning of contacting surfaces reduced but did not eliminate the presence of crystals after die-cutting.

A successful process for the prevention of the formation of the scopolamine hydrate crystals was ultimately discovered and is described in U.S. Patent No. 4,832,953, incorporated in its entirety herein by reference. According to that invention, formation of crystalline hydrates in a liquid dispersion of a hydratable liquid in a non-aqueous, typically polymeric, matrix can be prevented if, after they have been placed in their packages, the articles are heated to a temperature above the melting point of the crystalline hydrate, are maintained at that temperature for a period of time and then are allowed to cool to ambient conditions. For this process to be successful, holding times for cast films and laminates, prior to die-cutting, pouching, and annealing, were minimized in an effort to outrace the kinetics of crystal growth. It was found that when so treated, crystals initially present disappeared, did not reform upon cooling to ambient conditions, and there were no additional signs of crystal formation or growth after storage at ambient conditions and under accelerated aging conditions for several months.

The commercial manufacture of the product including the step of annealing the pouched systems as described in U.S. Patent No. 4,832,953 was then carried out for approximately seven years before the current crystallization problem developed and commercial production again had to be halted. The measures employed to prevent formation of the hydrate as taught in the 4,832,953 patent are not effective in preventing the formation of the newly observed crystals because: 1) the new crystals do not melt at the annealing temperatures specified therein; and 2) the kinetics of the new

1 crystal growth are significantly faster, such that films cannot practically be
2 moved through the manufacturing process fast enough to eliminate significant
3 crystal growth. Crystals have been observed only four hours after film casting
4 and have been observed in the final product.

5 An extensive investigation was undertaken, including examination of
6 raw materials, process equipment, and procedures to isolate a source of
7 crystallization, during which it was determined that crystal formation could not
8 be attributed to any specific feature of the procedures, equipment, or raw
9 materials used to produce the product. It was confirmed that rapid
10 crystallization could start after any manufacturing step involving the
11 scopolamine films and laminates. Production was halted until the problem
12 was solved according to this invention

13 14 SUMMARY OF THE INVENTION

15
16 The new crystal has been identified as a crystalline form of anhydrous
17 scopolamine base. The cause of the change from the previous hydrate form
18 to a more stable anhydrous crystal form is unknown. The inventors have
19 found that the annealing of all the individual scopolamine-containing films and
20 laminates, in addition to the final laminate and pouched system, successfully
21 prevents the formation and growth of the currently observed scopolamine
22 crystalline structure. The invention provides a method to effectively beat the
23 crystal growth kinetics in a practical manner.

24 It is accordingly an aspect of this invention to prevent the formation
25 and / or growth of a crystalline structure in a dispersion of a liquid in an
26 aqueous or non-aqueous matrix.

27 It is another aspect of this invention to prevent the formation and / or
28 growth of a crystalline structure of scopolamine in dispersions of scopolamine
29 base in a non-aqueous matrix.

1 It is another aspect of this invention to manufacture transdermal
2 therapeutic systems for the controlled delivery of scopolamine base which are
3 free from crystals of scopolamine.

4 It is yet another aspect of this invention to provide an improved method
5 of manufacture of transdermal therapeutic systems which prevents the
6 formation and / or growth of a crystalline structure in dispersions of a liquid in
7 an aqueous or non-aqueous matrix.

8 These and other aspects of this invention will be readily apparent from
9 the following description of the invention.

10 11 BRIEF DESCRIPTION OF THE DRAWINGS

12
13 Figure 1 is a flow diagram depicting the process of forming the
14 drug reservoir / backing layer according to a preferred embodiment of
15 this invention.

16 Figure 2 is a flow diagram depicting the process of forming the
17 rate control membrane / contact adhesive layer according to a preferred
18 embodiment of this invention.

19 Figure 3 is a flow diagram depicting the process of forming the final
20 laminate according to a preferred embodiment of this invention

21 Figure 4 is an isometric view of an in-line annealing oven useful for
22 the purposes of the present invention

23 24 DISCLOSURE OF THE INVENTION

25
26 According to this invention, formation and/or growth of a crystalline
27 structure in a dispersion of a liquid in an aqueous or non-aqueous matrix can
28 be prevented if, immediately following the formation of each and every film or
29 laminate of the dispersion, the layer(s) containing the liquid dispersion is (are)
30 sandwiched between non-porous films and subjected to an annealing process
31 wherein they are heated to a sufficient temperature for a sufficient time and

1 then allowed to cool. Preferably, the following conditions are satisfied at each
2 annealing step: 1) the melting point temperature of the crystal is exceeded;
3 2) sufficient time is provided to allow the crystal to melt; 3) the dispersion
4 is protected from environmental exposure until the next manufacturing
5 (and annealing) step; and 4) the annealing step begins promptly after film
6 formation and / or lamination. Films and laminates treated by this annealing
7 process are stable and have been observed to remain crystal-free after
8 storage at ambient conditions for at least 90 days.

9 A preferred embodiment of this invention is directed to the manufacture
10 of transdermal delivery devices. It has been found that transdermal delivery
11 devices manufactured according to this invention are free from crystals and
12 exhibit release rates within applicable specifications for the product. Although
13 this invention will be described with respect to a specific example relating
14 to the manufacture of transdermal delivery devices for the controlled delivery
15 of scopolamine, it should be recognized that this invention is applicable to
16 the processing of dispersions of any liquid agent capable of forming a
17 crystalline structure.

18 According to this preferred embodiment, individual films and laminates
19 of a transdermal therapeutic system which comprise a dispersion of a liquid in
20 a matrix, as well as the final laminate and pouched system, are subjected to
21 an annealing process immediately following the formation of the films or
22 laminates. The annealing process is performed immediately after the film is
23 placed between two non-porous substrates in order to minimize exposure of
24 the film to the atmosphere. The film or laminate thus treated is stable with
25 respect to crystal growth until the next processing step, assuming exposure of
26 the annealed film to the environment is controlled.

27 In a particularly preferred embodiment directed to the manufacture of
28 transdermal delivery devices containing scopolamine, the rate control
29 membrane / contact adhesive films, drug reservoir films, and final laminate
30 films are protected between two non-porous substrates and are subjected to
31 an annealing process, immediately following lamination, and are heated to a

1 sufficient temperature, for a sufficient time, and then allowed to cool to
2 ambient conditions in order to prevent subsequent crystal formation and
3 growth. The final laminate is then cut into individual systems, placed into
4 sealed containers, and then subjected to an additional annealing step.

5 The formation of the films and laminates may be achieved by any
6 means known in the art. Although this invention will be described with
7 respect to an example wherein a solvent casting procedure is utilized to form
8 the various films, it should be recognized that other procedures for forming
9 the films, such as extrusion or reverse roll coating, may be used in the
10 practice of this invention. For example, if an extrusion process is used to
11 form the various films, it would not be necessary to use the drying ovens in
12 the manufacturing processing line and the extruded films would proceed
13 directly to the annealing oven or to a lamination stage immediately followed
14 by the annealing step of this invention.

15 The annealing of the films and laminates can be achieved by
16 various means. For example, when the films are formed by solvent casting,
17 annealing can be performed by a second pass through the drying ovens that
18 are used to dry the initial film. This requires that by the time the last portion of
19 film has exited the ovens for the first time, the portion of film that first exited
20 the ovens has not already begun to crystallize. Alternatively, the film casting
21 may be broken up into small sublots so that any film or laminate is subjected
22 to annealing within a few hours of casting or lamination. Preferably,
23 annealing occurs in-line, immediately following film formation and/or
24 lamination. Most preferably, an annealing oven is placed immediately after
25 the lamination stage.

26 The manufacture of transdermal delivery devices using a solvent
27 casting procedure will now be described with reference to the drawings.
28 The process for the formation of the drug reservoir layer is shown in Figure 1.
29 The drug reservoir casting solution is cast onto impermeable backing layer 21
30 fed from source roll 11 to form a film comprising drug reservoir layer 22 on
31 impermeable backing layer 21. The film is then passed through the drying

1 ovens 20 to evaporate the solvent. The dried film is then passed through a
2 laminator 30 where non-porous interleaving layer 32 is applied to the surface
3 of drug reservoir layer 22. The laminate is then passed through in-line
4 annealing oven 40, shown in detail in Figure 4. After exiting the annealing
5 oven, the laminate is wound up on take-up roll 31 of the laminator.

6 The rate control membrane / contact adhesive layer is formed by a
7 similar process as shown in Figure 2. The contact adhesive solution 51 is
8 cast onto release liner 50 and passed through the drying ovens 20. Rate
9 control membrane 52 and non-porous interleaving layer 53 are then
10 laminated to the surfaces of the contact adhesive and rate control membrane,
11 respectively. The laminate is then passed through the in-line annealing oven
12 40 before being taken up on the take-up roll 31 of the laminator.

13 The final laminate is produced as shown in Figure 3. The drug
14 reservoir laminate and rate control membrane / contact adhesive laminate
15 rolls are set up in the laminator. Interleaving layer 53 is removed from the
16 rate control membrane / contact adhesive laminate and interleaving layer 32
17 is removed from the drug reservoir laminate, exposing the rate control
18 membrane 52 and drug reservoir 22, respectively, which are then laminated
19 together to form the final laminate. The final laminate, comprising
20 impermeable release liner 50, contact adhesive layer 51, rate control
21 membrane 52, drug reservoir layer 22, and impermeable backing layer 21,
22 is then passed through in-line annealing oven 40 before being taken up
23 once again on take-up roll 31 of the laminator. In a final processing step
24 (not shown), individual systems are die cut from the final laminate. The
25 systems are placed in individual pouches, the pouches are heat sealed and
26 the pouched systems are then placed in an in-line annealing oven for a final
27 annealing process.

28 Figure 4 depicts annealing oven 40 in greater detail. The laminate first
29 enters the annealing oven where it contacts heated roll 41 which provides
30 immediate heating to the laminate. The laminate passes over idler rolls 42
31 and tension roll 43 and is passed through the annealing chamber 44 which is

1 preheated to a predetermined temperature. The dwelling time of the laminate
2 in the annealing chamber may be adjusted by setting an appropriate line
3 speed for the laminate. Annealing oven 40 is also provided with air handler
4 45 and access door 46.

5 As seen in the above description, at each film forming / laminating
6 step, the adhesive is sandwiched between non-porous substrates so that
7 after annealing is performed, additional contamination by crystal seeds is not
8 possible until the next processing operation. After each intermediate film or
9 laminate is annealed, that product is stable until the next operation, as long
10 as it is not exposed to the atmosphere.

11 The use of an in-line annealing oven offers several advantages to
12 alternative methods of annealing individual films and laminates. First, it
13 eliminates the need for breaking the production down into small sublots in
14 order to reduce film exposure time, thus allowing for production at the
15 previous full lot capacity. Such a method also reduces the film exposure time
16 more effectively to only a matter of seconds. Additionally, the use of an
17 in-line annealing oven allows for better utilization of the casting ovens and
18 avoids the difficulty in handling the laminates as would be required if they
19 were to be run through the casting ovens a second time. With the in-line
20 annealing method of this invention, better prevention of crystal formation
21 is observed because only seconds elapse between the time that the film
22 leaves the casting ovens and enters the annealing oven, effectively beating
23 crystal growth kinetics by eliminating any time available for crystal formation
24 and / or growth.

25 The temperature and time are not critical provided they are adequate
26 to prevent the formation of crystals after cooling and are not so high as to
27 cause damage to the individual films or laminas. If crystals are initially
28 present, the temperature must be at, and preferably above, the melting point
29 of the crystal and the time should be sufficient to cause melting of all the
30 crystals present. If crystals are not present at the time of the heating step,
31 temperatures lower than the melting point of the crystal may be effective.

Nevertheless, it is preferable from the point of quality assurance and uniformity of processing conditions to heat above the melting point of the crystal, the formation of which it is desired to prevent.

In the preferred embodiment of this invention directed to the prevention of the formation of scopolamine crystals during the manufacture of transdermal therapeutic systems containing scopolamine, the temperature to which the individual and final laminates were heated is preferably within the range of 75-90° C, for a duration of 2-10 minutes. The final pouched systems are preferably heated to a temperature of 75° C for a period of 4-24 hours. The actual temperature for other materials is easily determined by measuring the melting point of the crystal.

Having thus generally described our invention, the following specific example is provided to illustrate the invention. The example is not intended to limit the scope of the invention in any way. Unless otherwise indicated, parts are by weight.

EXAMPLE 1

Preparation of scopolamine base solution

Scopolamine base was formed by dissolving scopolamine hydrobromide in an aqueous sodium bicarbonate-sodium carbonate buffer solution. Sodium hydroxide was added until a pH of about 9.6 was reached at which point the scopolamine base precipitated from solution and was extracted with chloroform.

Preparation of casting solutions

20.0 parts high molecular weight PIB (Vistanex L-100, 1,200,000 viscosity average molecular weight), 26.1 parts low molecular weight PIB (Vistanex LM-MS, 35,000 viscosity average molecular weight), 41.7 parts mineral oil (10 cp at 25° C.) and 11.3 parts of scopolamine base were

1 dissolved in chloroform in a mixer to prepare the drug reservoir casting
2 solution used in forming the drug reservoir film.

3 To prepare the contact adhesive casting solution, a solution of 23.1
4 parts of said high molecular weight PIB, 28.8 parts of said low molecular
5 weight PIB, 46.1 parts of said mineral oil, and 2.0 parts of said scopolamine
6 base were dissolved in chloroform in a mixer.

7 Preparation of films and laminates

8 The drug reservoir casting solution was then solvent cast to form a
9 drug reservoir film approximately 50 micrometers dry thickness on an
10 approximately 65 micrometer backing of aluminized polyethylene
11 terephthalate (Scotchpak ®). The drug reservoir film was passed through an
12 oven to evaporate the chloroform, leaving behind a drug containing adhesive
13 film on a backing substrate. After leaving the oven, the film was moved to a
14 laminator where an interleaving film was applied. The laminate was then
15 passed into a second oven placed immediately following the laminator,
16 where the laminate was heated to a temperature of 80-85° C for 9-10
17 minutes. Thereafter, the laminate is returned to the take-up roll on the
18 laminator.

19 The rate control membrane / contact adhesive laminate was similarly
20 prepared by solvent casting a 50 micrometer dry thickness adhesive layer of
21 the contact adhesive casting solution onto a 75 micrometer siliconized,
22 polyethylene terephthalate film. After casting, the films were passed through
23 the ovens to evaporate the chloroform solvent, leaving behind a drug
24 containing adhesive on a release liner. This film was moved to a laminator,
25 where a microporous polypropylene rate controlling membrane, with the
26 pores saturated with mineral oil, was laminated to the adhesive surface.
27 An interleaving film was added to protect the top of the control membrane
28 and the entire laminate was introduced into the second oven immediately
29 thereafter and was heated to a temperature of 80-85° C for 5-6 minutes.

1 The rate control membrane surface of the rate control membrane /
2 contact adhesive laminate was then laminated to the drug reservoir surface
3 of the drug reservoir laminate to yield a final laminate. This final laminate
4 was then also passed through the annealing oven immediately following
5 the laminator and heated to a temperature of 80-85° C for approximately
6 2 minutes. 2.5 cm² circular disk-shaped systems were punch-cut from the
7 resulting five layer laminate. The individual systems were then packaged
8 within heat-sealed foil-lined pouches. The pouches were then treated by
9 heating in an additional annealing oven to 75° C for 4-24 hours and thereafter
10 allowed to cool to ambient conditions.

11 None of the systems made according to the invention were observed
12 to contain crystals. Additionally, systems made according to the invention
13 exhibited release rates within the applicable specifications for the product.

14 Having thus described our invention, it is readily apparent that various
15 modifications can be made by workers skilled in the art without departing from
16 the scope of this invention. It is intended that the invention embrace these
17 equivalents within the scope of the claims that follow.

1 We claim:

2

3 1 An improved method for manufacturing delivery devices for the
4 transdermal administration of a liquid drug capable of forming a crystalline
5 structure, the method comprising.

6 a) heating, to a predetermined temperature, each individual
7 film or laminate of a transdermal delivery device which comprises a dispersion
8 of said liquid drug in a matrix immediately following film formation or
9 lamination,

10 b) maintaining each film or laminate at the desired
11 temperature for a period of time sufficient to prevent the formation and/or
12 growth of a crystalline structure in any film or laminate; and

13 c) allowing each film or laminate to cool to ambient
14 conditions.

15 2. The method according to claim 1 further comprising the step of
16 providing that each dispersion of said liquid drug in a matrix is placed
17 between two non-porous substrates prior to heating

18 3 The method according to claim 2 further comprising the steps of:

19 c) laminating the individual films or laminates to form a final
20 laminate;

21 d) heating the final laminate to said predetermined
22 temperature immediately following lamination and maintaining the final
23 laminate at the temperature for a period of time sufficient to prevent formation
24 and/or growth of a crystalline structure in the final laminate; and

25 e) allowing the final laminate to cool to ambient conditions.

26 4 The method according to claim 3 further comprising the steps of:

27 e) cutting subunits from said final laminate and forming said
28 delivery devices;

29 f) packaging said delivery devices in sealed containers;

1 g) heating the devices in said containers to a predetermined
2 temperature and maintaining the devices at the temperature for a period of
3 time sufficient to prevent formation and/or growth of a crystalline structure in
4 the devices; and

5 h) allowing the sealed devices to cool to ambient conditions.

6 5. The method according to claim 3 wherein the predetermined
7 temperature is above the melting point of the crystalline structure and the
8 period of time is sufficient to melt any crystals present in the dispersion.

9 6 The method according to claim 1 wherein the device comprises
10 an impermeable backing lamina, a drug reservoir layer, a release rate
11 controlling layer, and adhesive layer, and a release liner layer and said
12 dispersion forms said drug reservoir layer.

13 7. The method of claim 6 wherein the dispersion forms said
14 adhesive layer.

15 8. The method of claim 2 wherein the drug is scopolamine.

16 9. The method of claim 8 wherein the predetermined temperature
17 is within the range of 75-90° C and the period of time is 2-10 minutes.

18 10. The method of claim 4 wherein the liquid drug is scopolamine
19 and the devices sealed within the containers are heated to a temperature of
20 about 75° C for a period of approximately 4-24 hours.

21 11. A process for preventing the formation of the crystalline
22 structure of a liquid drug dispersed within a matrix which comprises:

23 a) forming a laminate wherein each individual film or lamina
24 comprising a dispersion of said liquid drug in a matrix is heated to a
25 predetermined temperature immediately following formation or lamination;

26 b) maintaining each film or lamina at the desired
27 temperature for a period of time sufficient to prevent the formation and/or
28 growth of a crystalline structure in any film or lamina; and

29 c) allowing each film or lamina to cool to ambient conditions.

12 A process according to claim 11 further comprising the step of providing that each dispersion of said liquid drug in a matrix is placed between two non-porous substrates prior to heating.

13 A process according to claim 12 wherein the predetermined temperature is above the melting point of the crystalline structure and the period of time is sufficient to melt any crystals present in the dispersion.

14 An improved method of manufacturing delivery devices for the transdermal administration of a liquid drug capable of forming a crystalline structure, comprising:

a) forming a drug reservoir / backing film, said drug reservoir comprising a liquid drug capable of forming a crystalline structure;

b) immediately following forming the drug reservoir / backing film, performing a first annealing step wherein the drug reservoir / backing film is heated to a predetermined temperature for a period of time sufficient to prevent formation and/or growth of a crystalline structure and thereafter allowed to cool to ambient conditions;

c) forming a contact adhesive / release liner film, said contact adhesive comprising a liquid drug capable of forming a crystalline structure;

d) immediately following forming the contact adhesive / release liner film, performing a second annealing step wherein the contact adhesive / release liner film is heated to a predetermined temperature for a period of time sufficient to prevent formation and/or growth of a crystalline structure and thereafter allowed to cool to ambient conditions;

e) laminating the drug reservoir surface of the drug reservoir / backing film to the contact adhesive surface of the contact adhesive / release liner film to form a final laminate;

f) immediately following forming the final laminate, performing a third annealing step wherein the final laminate is heated to a predetermined temperature and maintaining the temperature for a period of time sufficient to prevent the formation and/or growth of a crystalline structure

1 in the final laminate and thereafter allowing the final laminate to cool to
2 ambient conditions.

3 15. The method according to claim 14 further comprising the steps
4 of: placing a non-porous substrate on the drug reservoir
5 surface of said drug reservoir / backing film prior to said first annealing step;
6 placing a non-porous substrate on the contact adhesive
7 surface of said contact adhesive / release liner laminate prior to said second
8 annealing step; and
9 removing the non-porous substrates from said drug
10 reservoir / backing film and said contact adhesive / release liner film prior to
11 laminating the drug reservoir surface of the drug reservoir / backing film to the
12 contact adhesive surface of the contact adhesive / release liner film to form
13 the final laminate.

14 16. The method according to claim 15 wherein the predetermined
15 temperature is above the melting point of the crystalline structure and the
16 period of time is sufficient to melt any crystals present in the dispersion.

17 17. The method according to claim 16 further comprising the
18 steps of:
19 cutting subunits from said final laminate and forming said
20 delivery devices;
21 packaging said delivery devices in sealed containers;
22 heating the devices in said containers to a predetermined
23 temperature and maintaining the devices at the temperature for a period of
24 time sufficient to prevent formation and/or growth of a crystalline structure in
25 the devices; and

26 allowing the sealed devices to cool to ambient conditions.

27 18. The method according to claim 14 further comprising the step of
28 laminating a rate control membrane to the contact adhesive surface of the
29 contact adhesive / release liner film to form a rate control membrane / contact
30 adhesive / release liner laminate prior to said second annealing step.

19 The method according to claim 18 further comprising the
steps of
placing a non-porous substrate on the drug reservoir
surface of said drug reservoir / backing film prior to said first annealing step;
placing a non-porous substrate on the surface of the rate
control membrane prior to said second annealing step; and
removing the non-porous substrates from said drug
reservoir / backing film and said rate control membrane / contact adhesive /
release liner laminate; and
laminating the drug reservoir surface of the drug reservoir
/ backing film to the surface of the rate control membrane of the rate control
membrane / contact adhesive / release liner laminate to form the final
laminate.

20 The method according to claim 19 wherein the predetermined
temperature is above the melting point of the crystalline structure and the
period of time is sufficient to melt any crystals present in the dispersion.

21 The method according to claim 20 further comprising the
steps of:
cutting subunits from said final laminate and forming said
delivery devices;
packaging said delivery devices in sealed containers;
heating the devices in said containers to a predetermined
temperature and maintaining the devices at the temperature for a period of
time sufficient to prevent formation and/or growth of a crystalline structure in
the devices; and
allowing the sealed devices to cool to ambient conditions.

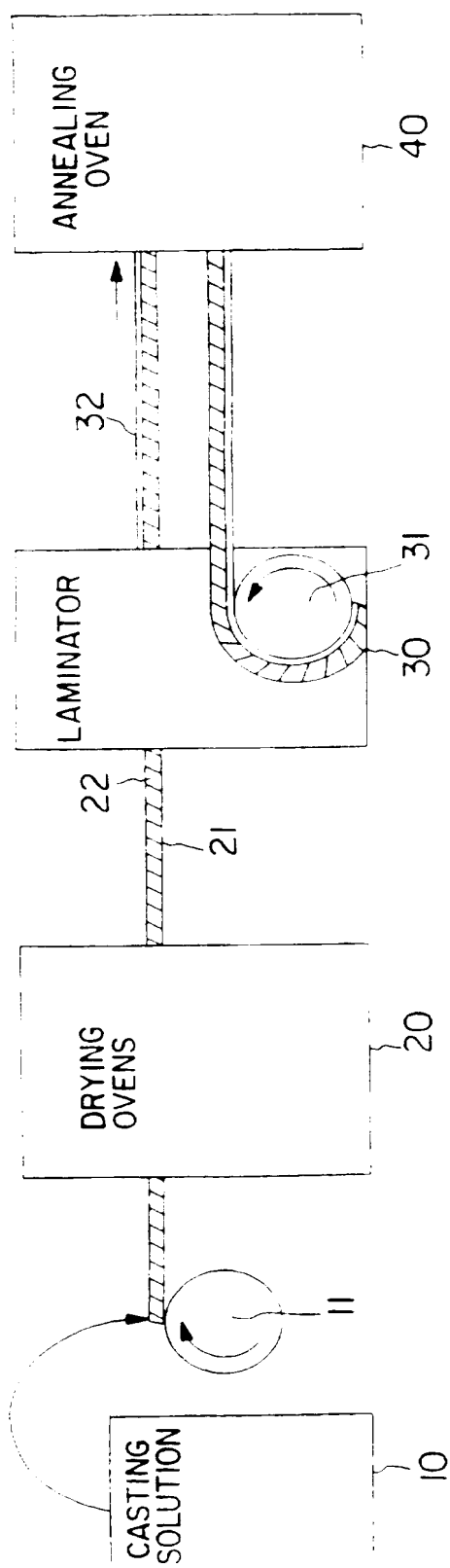
22 The method according to claim 18 wherein the rate control
membrane is a microporous polypropylene membrane saturated with
mineral oil.

23 The method according to claim 21 wherein the liquid drug is
scopolamine base.

1 24. The method according to claim 23 wherein the predetermined
2 temperature in the first, second, and third annealing steps is approximately
3 75-90° C and the period of time is about 2-10 minutes.

4 25 The method according to claim 24 wherein the devices sealed
5 within the containers are heated to a temperature of about 75° C for a period
6 of approximately 4-24 hours.

7 26. A drug delivery device for the transdermal administration
8 of scopolamine manufactured by the method according to any one of
9 claims 1, 14, or 25.



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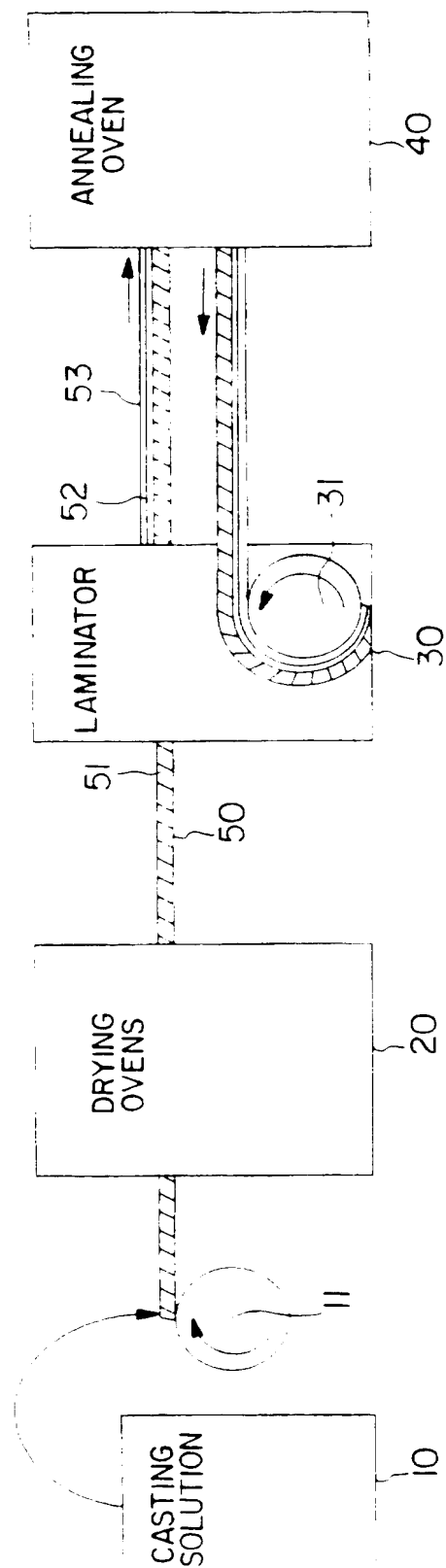


FIG. 2

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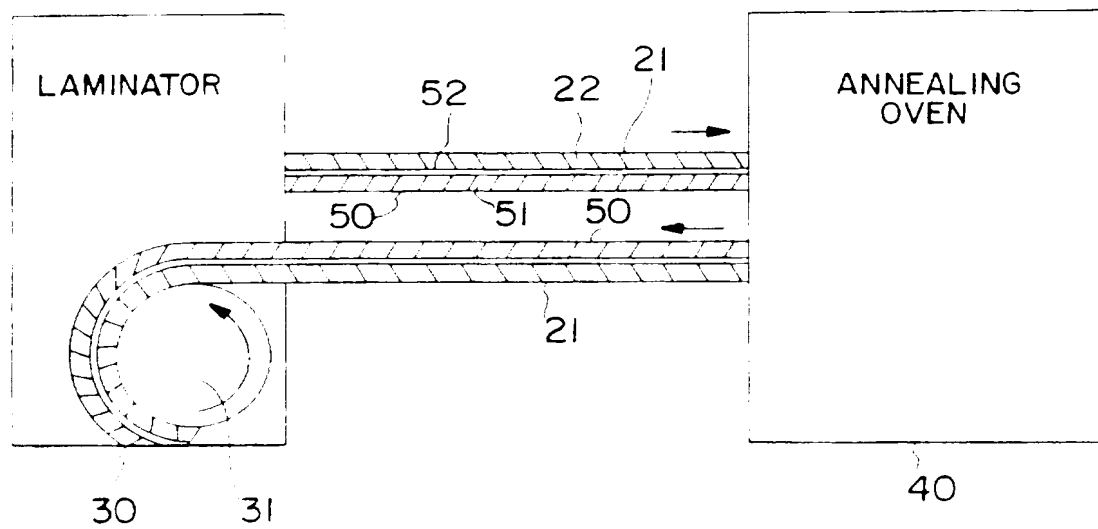


FIG. 3

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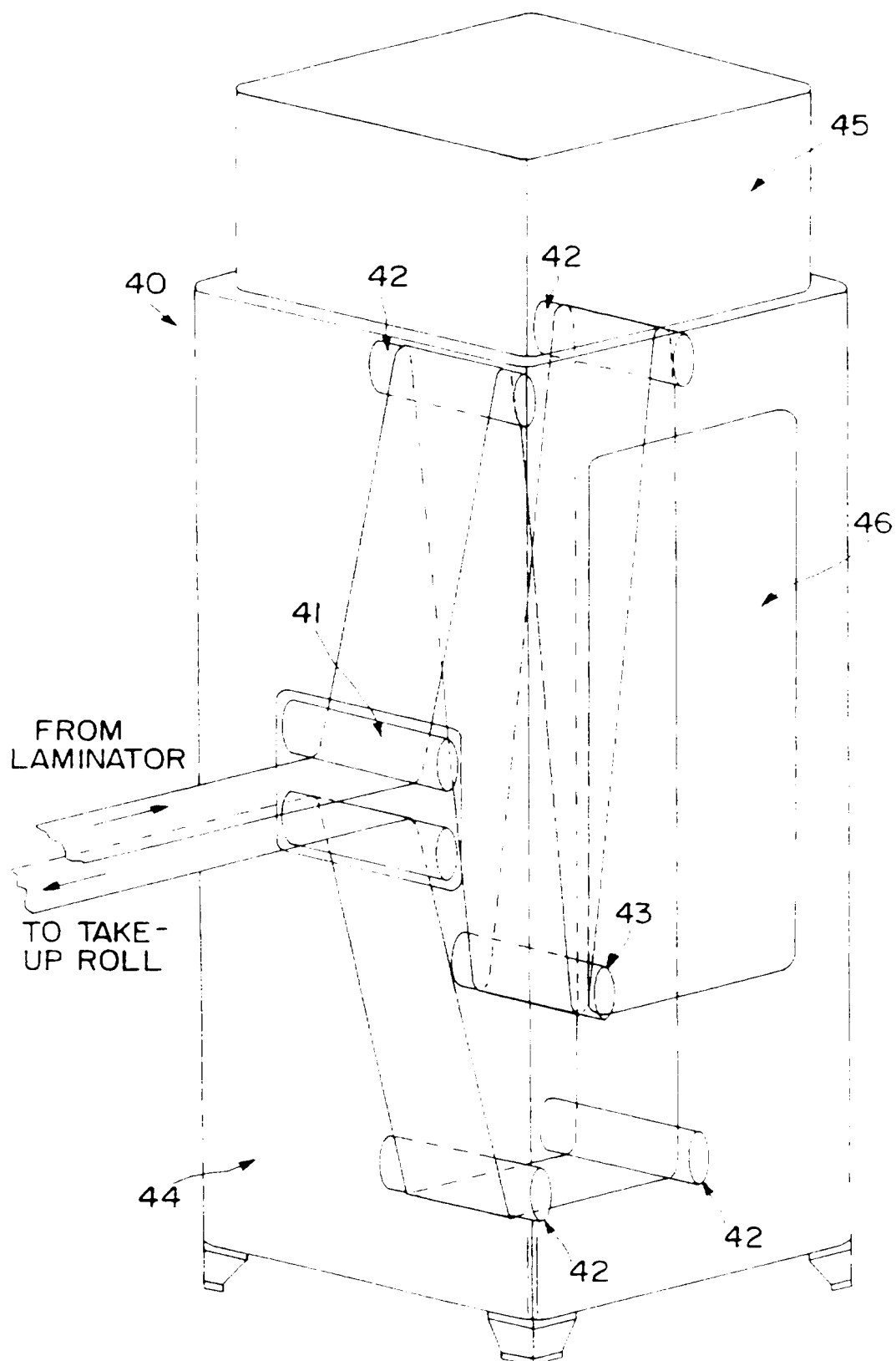


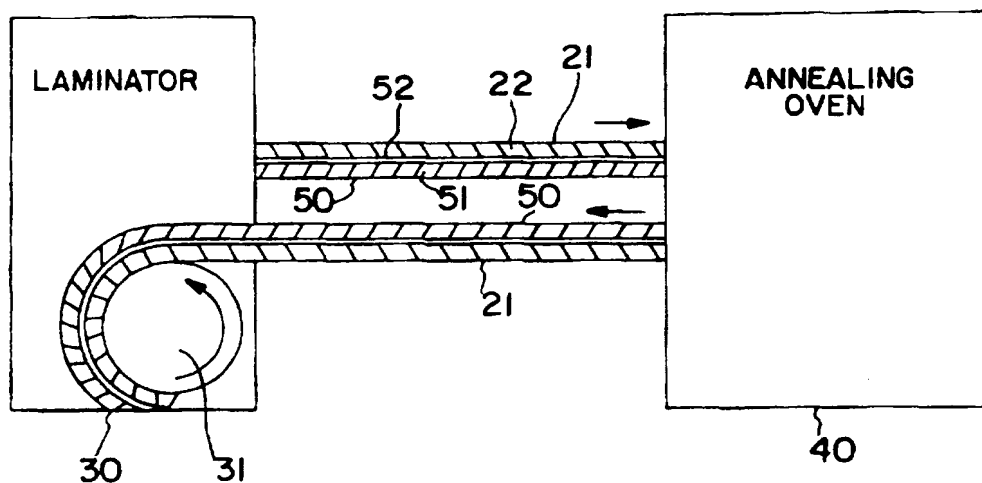
FIG. 4



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(21) International Application Number: PCT/US96/18397 (22) International Filing Date: 15 November 1996 (15.11.96) (30) Priority Data: 08/566,228 1 December 1995 (01.12.95) US (71) Applicant: ALZA CORPORATION [US/US]; 950 Page Mill Road, P.O. Box 10950, Palo Alto, CA 94303-0802 (US). (72) Inventors: DOHNER, John, W.; 24 Arastradero Road, Portola Valley, CA 94028 (US). BURA, Scott, A.; 1518 Clarita Avenue, San Jose, CA 95130 (US). (74) Agents: RAFA, Michael, J. et al.; Alza Corporation, 950 Page Mill Road, P.O. Box 10950, Palo Alto, CA 94303-0802 (US).		(81) Designated States: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i> (88) Date of publication of the international search report: 14 August 1997 (14.08.97)

(54) Title: IMPROVED METHOD FOR PREVENTING CRYSTAL FORMATION IN A DISPERSION OF A LIQUID IN A MATRIX

**(57) Abstract**

An improved method for the manufacture of transdermal drug delivery devices comprising liquid dispersions of a liquid in an aqueous or nonaqueous matrix is disclosed. More particularly, the invention relates to preventing the formation of a crystalline structure in such liquid dispersions by annealing films and laminates in-line immediately following film formation and/or lamination during the manufacture of these devices.

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INTERNATIONAL SEARCH REPORT

International Application No.

PCT/US 96/18397

A. CLASSIFICATION OF SUBJECT MATTER
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According to International Patent Classification (IPC) or to both national classification and IPC

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Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

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C. DOCUMENTS CONSIDERED TO BE RELEVANT

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A	US 4 308 621 A (MENDELSON JERRY M) 29 December 1981 see column 4; example 1 ---	1-25
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Date of the actual completion of the international search

29 May 1997

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